ELECTRONARCOSIS BY DIRECT STIMULATION OF THE BRAIN STEM

ASAI, SHIGEZO

原　　著

ELECTRONARCOSIS BY DIRECT STIMULATION OF THE BRAIN STEM

by

Shigezo Asai

From the 1rst Surgical Division, Kyoto University Medical school
(Director . prof. Dr. Chisato Araki)
Received for Publication Spt. 29. 1957

INTRODUCTION

This report constitutes a link of a series of experimental studies on disturbance of consciousness which have been made in our laboratory since 1944.

I applied Yoshii's method of "electronarcosis with no convulsive phase by means of 60 cps alternating current" (Yoshii, 1953) directly to various parts of the brain of unanesthetized cats.

MATERIALS AND METHODS

(1) Unanesthetized adult cats weighing from about 2 to 3 kg. were used for experiments.

(2) In preliminary experiment, gradually increasing 60 cps alternating current was applied to the temporal region on both sides according to Yoshii's method through two steele needle electrodes which had been inserted to the level of dura passing through the skull at the point just above the porus acusticus externus, one electrode on each side.

(3) Bipolar stimulating electrode to be inserted into the brain consisted of two card clothing wires of about 0.2 mm in diameter, each of which was insulated and fixed to each other by means of Cemedine No. 240 and white lacquer except from 0.3 to 0.5 mm length of the tip. The bipolar electrode was about 0.6 mm in diameter, about 20 cm in length, and the distance between two poles was about 0.1 mm.

(4) Electrical stimulation was effected by means of 60 cps A. C. which was supplied by the apparatus made by the author (cf. Fig. 1). Stimulation voltage used was under 10 volts, and was usually increased gradually.

(5) The cat was fixed on a hammock in prone position and the four limbs were allowed to hang down naturally, therefore any movement of the limbs and the state of muscular tension could be observed easily. After a suitable craniotomy was made in the parietal region under ether anesthesia, the Clarke's sterotaxic instrument (hang down type) was placed on the head of the cat. In full wakefulness fairly long after interruption of ether, the electrode was inserted into the brain for stimulation.

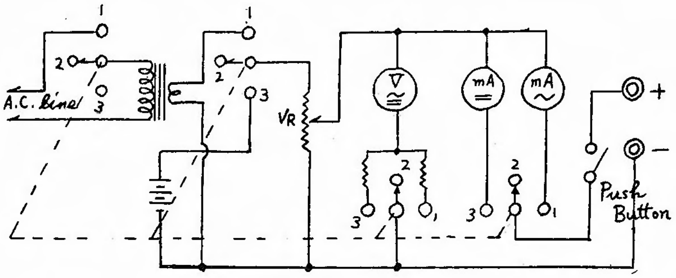


Fig. 1 Electrical stimulation apparatus. Rotary SW. Position: 1—A. C., 2—OFF, 3—D. C.

(6) After stimulation study was over, direct current of 4.5 volts was passed through the electrode to deposit iron.

(7) After physiological experiment was done, the cat was sacrificed by cutting both carotid arteries. The brain was fixed in 10 per cent formalin, embedded in celloidin and subjected to Nissl stain, myelin stain, and iron-carmine stain. Anatomical guide was obtained mainly from WINKLER and POTTER (1914) and NIIMI (1949, 1950) and reference was made also to JASPER (1949) and McLARDY (1951).

(8) Surface EEG was recorded with San-ei 2 channel portable electroencephalograph.

(9) Additional experiment was made in an attempt to see what change may happen in the electronarcosis induced by electrical stimulation of the mesencephalic central gray matter, as a result of transection of the rostral end of the midbrain, cranial to the stimulation point. In this experiment, the stimulation electrode had to be inserted into the brain before transection. The transection needed much care not to change the location of the electrode, so that an electrode was devised as shown in Fig. 2, which was freely movable in accordance with possible movements

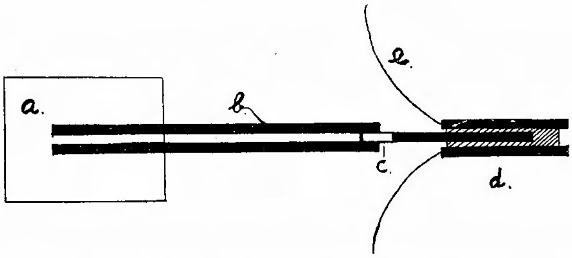


Fig. 2. The stimulation electrode specifically devised for transection experiment.
a: The ebonite board to fix the electrode: attached to the Clarke's stereotaxic instrument.
b: The holder of the electrode.
c: By soldering the holder is connected with the electrode.
After insertion of the electrode has been done, this connection is separated by heating.
The separation of the electrode from the holder serves to prevent movements of the electrode simultaneous with transection.
d: The electrode. The length 1.3 cm, otherwise the same as the ordinary electrode.
e: Fine enamelled wire.

of the brain tissue during the procedure of transection. In doing transection, superior sagittal sinus was ligated and dura was incised. Then under the guide of the Clarke's stereotaxic instrument, the transection was executed at the rostral end of the midbrain by means of a nkife which was attached to the electrode holder of the instrument. Preliminary confirmation should have been made that the electronarcosis could be effected by electrical stimulation of a certain locus in the brain stem. Then transection was made, and the same locus was stimulated again.

RESULTS

(I)

Preliminary experiment of electronarcosis following YOSHII's extradural method. As the stimulation voltage increased, the cat writhed and moved violently, but when the voltage reached about 3-4 volts, the animal became quiet, the pupils were fully dilated, and the corneal reflex as well as responses to painful stimuli applied to the auricule, to the nose tip, to the nasal septa, and to the pharynx, disappeared. Muscles of the limbs relaxed, and the cat did not react to heat at his pads. The state corresponded precisely to the YOSHII's electronarcosis.

(II)

Electronarcosis by direct stimulation of various parts of the brain. Midbrain was preferentially stimulated, but stimulation was applied also to thalamus, hypothalamus and anterior cingulate gyrus etc..

(1) Influences of mere insertion of the electrode on animal's behavior.
In most cases no distinct changes were induced in behavior by mere insertion of the electrode into the brain except for some restlessness, some mews, and/or anisocolia. However, some cats cried violently when the electrode hit certain cerebral loci, of which electrical stimulation usually induced more intense cry and more violent actions. These loci were found histologicaly to be lateral to the mesencephalic aqueduct.

(2) Classification of behaviors.
During electrical stimulation, cats showed various behaviors according to varying loci stimulated, to increase in stimulation voltage, and to duration of stimulation. The behaviors were divided into following six types.

1) Coma type (complete electronarcosis)
Mydriasis (+); corneal reflex (−); pupillary reaction to light (−); pharyngeal reflex (−); auricular reflex (−); sneezing reflex to naso-septal stimuli (naso-septal reflex) (−); avoiding reaction to heat at the auricle or at the nose tip (−); relaxation of muscles of the body trunk and the four limbs (+); withdrawal reflex to painful stimuli or touch stimuli given to any part of the body (−); patellar reflex (−) or (±).

2) Semicoma type (nearly complete electronarcosis)
Mydriasis (+); all or most of the above discribed reflexes observable at the head and face (−); relaxation of muscles of the trunk and the four

limbs (−); response to touch stimuli at any limb (+); that to painful stimuli at any limb (±) or (−).

The cats moved their four limbs on some occasions, but generally hung them down.

3) Sham rage type

All of the reflexes at the head and face (−), or some of them (+), or nearly all of them (+); muscle tonus of the trunk and the limbs was enhanced, and the cats writhed in screaming.

4) Kinetic excitation type.

All of the reflexes at the head and face (−), or some of them (+), or nearly all them (+); muscle tonus of the body trunk and the limbs was enhanced, or normal, and the cats moved their four limbs nearly continuously as if they were struggling. In some cases, response to painful stimuli at any limb was exaggerated.

5) Convulsion type

Tonic or clonic convulsions (+).

6) Type showing no behavioral change.

In some cases of this group, mydriasis was observed.

(3) Classification of the experimental cases.

Except in the group showing no behavioral changes, no consistent type of behavior lasted throughout the stimulation period, and the increase in stimulation voltage usually caused behavioral change from one type to another.

The coma type and the semicoma type were preceded by the kinetic excitation type in all cases except one in which coma was elicited from the beginning.

In regard to the sham rage type, some cases showed this type from the beginning and others showed this after the kinetic excitation type.

The convulsion type was seen from the beginning in one case, in which, however, the kinetic excitation type followed.

In another case, the convulsion type occurred together with the sham rage type.

Thus, all the experimental cases were classified into following 6 groups, having respective characteristics in the reactions to stimulation.

Group 1: Cases showing the coma type without any preceding convulsion.
Group 2: Cases showing the semicoma type without any preceding convulsion.
Group 3: Cases showing only the sham rage type throughout or showing this after the kinetic exciation.
Group 4: Cases showing only the kinetic excitation type.
Group 5: Cases showing the convulsion type.
Group 6: Cases showing no behavioral change.

(4) Illustrating cases of each group.

Group 1:

Cat 2. Female, 2.5 kg. 1st puncture on the right side of the midbrain.

5° 10′ 0″	Onset of electrical stimulation	
5″	0.5 v. about 0.01 mA	Stiffens the body.
15″		Mydriasis appears; urinates.
30″	1.0 v. 0.1 mA	Mydriasis is present; corneal reflex (±); moves the limbs lightly.
11′ 20″	1 6 v. 0.15 mA	Moves the forelegs lightly; corneal reflex (±).
12′		Mews mildly; corneal reflex (±); auricular reflex (−); pharyngeal reflex (±); reaction to pinch at the nose tip (−).
12′ 15″	2.2 v. 0.4 mA	Stops mewing; does not respond to heating at the nose tip.
13′	2.8 v. 0.65 mA	Moves the left foreleg a little.
14′	3.8 v. 1.5 mA	Corneal reflex (−); pharyngeal reflex (−); still moving the left foreleg a little.
15′	4.0 v. 2.4 mA	State corresponding to the coma type.
17′	5.0 v. 2.6 mA	The same.

Cat 17. Female, 2.7 kg. 1st puncture on the left side (midbrain).

12° 5′	Onset of stimulation	With increase in stimulation voltage, mydriasis appears; corneal reflex (±).
15′ 20″	1.0 v. about 0.01 mA	Maximal mydriasis; urinates; state corresponding to the coma type.
18′	1.0 v. about 0.01 mA	Relaxes the jaw-joint; corneal reflex (±); raises the claws.

Group 2:

Cat 7. Female, 2.2 kg. 4th puncture on the right side (midbrain).

3° 35′	Onset of stimulation	With increase in stimulation voltage, mydriasis appears; mews lightly.
	1.0 v. about 0.01 mA	Corneal reflex (+); pharyngeal reflex (+); still mewing.
37′	1.5 v. 0.2 mA	Stops mewing and becomes quiet; corneal reflex (+).
	2.5 v. 0.5 mA	Moves the four limbs a little excitedly; corneal reflex (±); pharyngeal reflex (±); auricular reflex (±).
41′	3.0 v. 0.7 mA	Still moving the four limbs; maximal mydriasis; pupillary reaction to light (±).
	3.5 v. 1.3 mA	Still moving the four limbs; corneal reflex (−); auricular reflex (±).
44′	4.0 v. 1.7 mA	Still moving the four limbs; pharyngeal reflex (±); response to painful stimuli at the pad (+).

47′	4.0 v. 2.0 mA	Hangs down the four limbs naturally, and doesn't move them; the muscle tonus is normal.
50′	6.5 v. 2.0 mA	Corneal reflex (±); begins to mew lightly.

Group 3:

Cat 24. Male, 2.1 kg. 1st puncture on the right side (midbrain).

2° 50′	Onset of stimulation	Presently, spits, hisses and struggles.
	0.5 v. about 0.01 mA	Cries strongly and struggles; attacks and bites the pincette which is put in front of the mouth; whirls the tail like a windmill. Moderate mydriasis; corneal refled (±); pupillary reaction to light (+); pharyngeal reflex (+); auricular reflex (+).
	1.5 v. about 0.1 mA	Crying repeatedly; raises the claws; and struggles; whirls the tail; pharyngeal reflex (±); naso-septal reflex (±); bites any objects inserted in the mouth.
	2.0 v. 0.2 mA	Cries; corneal reflex (+); raises the claws.
	3.0 v. 0.3 mA	The same as before in appearance.
58′	5.0 v. 1.0 mA	The same.
	10.0 v. 1.1 mA	The same.

Group 4

Cat 22. Female, 2.7 kg. and puncture on the right side (midbraln).

1° 50′	Onset of stimulation	Mydriasis begins.
	1.5 v. 0.1 mA	Corneal reflex (±); pharyngeal reflex (±); auricular reflex (±); mews when nociceptive stimuli are applied to the nose tip; moves the four limbs excitedly; raises the claws; whirls the tail.
51′	2.0 v. 0.1 mA	Mydriasis is present; corneal reflex (−); auricular reflex (±); pharyngeal reflex (±); moves the limbs excitedly.
52′	2.5 v. 0.2 mA	Doesn't react to heat at the auricle and the nose tip; nasoseptal reflex (−).
53′	3.0 v. 0.2 mA	Pupillary reflex to light (−); pharyngeal reflex (−); auricular reflex (−), still moving the limbs excitedly.
55′	6.5 v. 1.5 mA	Similar in appearance.
	9.0 v. 2.0 mA	Current intensity doesn't increase over 2.0 mA; similar in appearance.
58′	9.0 v. 1.0 mA	Corneal reflex (+); auricular reflex (+); naso-septal reflex (+); mews; moves the four limbs a little, but withdraws and

raises the claws when touched at the pads.

Group 5

Cat 6. Female, 2.4 kg. 3rd puncture on the right side (midbrain).

10° 32′	Onset of stimulation	Mydriasis begins.
	1.0 v. 1.0 mA	Generalized tonic convulsion begins; maximal mydriasis; pupillary reaction to light (-); corneal reflex (−); pharyngeal reflex (−); auricular reflex (−); doesn't react to heat at the auricle and the nose tip.
33′	3.0 v. 2.0 mA	Still convulsion is persisting; similar in appearance.
	5.0 v. 2.5 mA	Tonic convulsion is no more observed; moves the four limbs excitedly; brisker response to stimuli at the limbs.
35′	5.0 v. 2.0 mA	The same.
36′ 30″	10.0 v. 4.0 mA	Current intensity doesn't increase over 4 mA. Similar in appearance; all the reflexes examined at the head and face are still absent.

Cat 11. Female, 2.3 kg. 2nd puncture on the right (midbrain).

12° 52′	Onset of stimulation	
53′	1.0 v. 0.5 mA	Mydrias is induced; then abruptly generalized tonic convulsion appears; urinates; after the convulsion is over, pupillary reaction to light is absent; corneal reflex (−); auricular reflex (−); attacks and bites the pincette put before the mouth; naso-septal reflex (±); reacts to heat at the nose tip; horizontal nystagmus is present; brisker response to stimuli at the limbs; reacts to heat at the limbs.
1° 4′	2.2 v. 1.0 mA	Generalized tonic convulsion same as before.
1° 5′	3.5 v. 2.0 mA	Convulsion continues for some time; after convulsion is over horizontal nystagmus is present; all the reflexes examined at the head and face are absent; somewhat brisker response to stimuli at the limbs.
1° 9′	3.5 v. 2.0 mA	Corneal reflex (+); pupillary reaction to light (−); auricular reflex (±); reacts to heat at the auricle (+); naso-septal reflex (+); attacks and bites the pincette put in front of the mouth.

Cat 13. Male, 3 kg. 1st puncture on the right (midbrain).

4° 40′ Onset of stimulation

	1.0 v. 0.2 mA	No change.
41′	2.0 v. 0.3 mA	Moves the body a little.
42′	3.0 v. 0.5 mA	Mydriasis is present; tonic convulsion of hindlegs appears; pupillary reaction to light (+); corneal reflex (+); pharyngeal reflex (+); naso-septal reflex (+).
46′	4.0 v. 0.8 mA	Convulsion still continues; begins to cry strongly; attacks the pincette put in front of the mouth; corneal reflex (+); naso-septal reflex (+); auricular reflex (+); reacts to heat at the auricle.
48,	5.0 v. 1.2 mA	Similar in appearance.
51′	6.2 v. 2.0 mA	Generalized tonic convulsion is extremely violent; transient apnea for 30 sec; corneal reflex (−); pupillary reaction to light (−); pharyngeal reflex (−); naso-septal reflex (−)
52′	6.2 v. 2.0 mA	All reactions (+); attacks the pincette put in front of the mouth.

Group 6

Cat 6. Female, 2.4 kg. 2nd puncture on the left side (midbrain).

4° 24′	Onset of stimulation	Pupils dilate at once.
25′	3.5 v. 1.5 mA	Shakes the head once; corneal reflex (+); pharyngeal reflex (+); auricular reflex (+); quiet; withdrawal reflex to touch at the limbs (+).
26′ 30″	10.0 v. 5.0 mA	Similar in appearance.
	10.0 v. 2.0 mA	Current intensity is decreased. Pupils are of normal size.

Cat 29. Male 2.6 kg. 2nd puncture on the left side (anterior cingulate gyrus).

10° 45′	Onst of stimulation	
47′	4.0 v. 0.5 mA	Quiet; all reflexes are positive; moves the body trunk and the four limbs when reflexes are examined; pupils are of normal size; at times spontaneous movements are observed.
	5.5 v. 1.0 mA	Similar in appearance.
49′	9.0 v. 2.0 mA	The same.
51′	10.0 v. 3.0 mA	The same.

(5) On stimulation dosage.

Cases showing each type of behavior have been classified according to stimulation dosage, voltage and intensity (cf. Table 1). Coma tended to be induced when stimulation voltage was from 3 to 6 volts, semicoma from 1 to 5 volts, and sham rage and convulsion under 1 volt. And coma was apt to occur when current intensity was under 3 mA, semicoma under 2 mA, and sham rage and convulsion

Table 1.

	-1v.	-2v.	-3v.	-4v.	-5v.	-6v.	-7v.	-8v.
Coma	1		1	2		3	1	
Semicoma		2	2	3	3			
Sham rage	10		1	1	1			1
Convulsion	8	2	1	1		1		

	-1mA	-2mA	-3mA	-4mA	-5mA	-6mA
Coma	2	2	3	1		
Semicoma	4	5	1			
Sham rage	12	1	1			
Convulsion	12					1

Incidence of each type of behavioral changes as seen with respect to stimulation voltage and currint intensity used.

Cases of coma and semicoma shown in this table are only those without any preceding convulsive phase.

under 1 mA.

Thus it is evident that optimal dosage of stimulation, by which the coma or the semicoma type with no convulsive phase is elicited, is higher than that by which the sham rage or the convulsion type is elicited.

(6) Coma and semicoma seen in cases of group 1 and 2 continued for from 3 to 4 minutes when the same stimulation voltage was kept up.

(7) Behavior of the animal following interruption of the electrical stimulation. In group 1 and 2, it was noted that the cats always restored their former behavioral state almost simultaneously with interruption of stimulation or at the latest 30 second after that. Also in group 3, 4 and 5 they restored their former behavior as quickly as in group 1 and 2, but the animals, which showed extreme kinetic phenomena during stimulation, seemed in most cases to be exhausted after interruption of stimulation. In such cases decrease in spontaneous movement persisted for a long time, and responsiveness to various stimuli was generally poor (although in some cases it was exaggerated).

(8) Effects on behavior of direct current passed through the electrodes. After stimulation experiments had been done, direct current with the intensity of 4.5 volts was transmitted for 20 seconds to loci previously stimulated in all the cases. However, this time the cats moved only slightly and no other observable behavioral change was exhibited.

(9) The sites of stimulation in each group. The sites of stimulation are as follows.

Group 1

Cat 32. The boundary between the ventromedial part of the mesencephalic central gray matter and the reticular formation at the level of comiissura posterior.

Cat 2. The boundary between the ventral part of the mesencephalic central gray matter and the reticular formation at the level of nucleus oculomotorius.

Cat 17. The ventrolateral part of the mesencephalic central gray matter at the level of nucleus oculomotorius.

Cat 12. Cat 25. The ventromedian part of the mesencephalic central gray matter near the aqueductus Sylvii at the level of nucleus trochlearis.

Cat 8. The ventrolateral part of the mesencephalic central gray matter caudal to the level of commissura corporis quadrigemini postici.

Cat 48. Cat 49. The ventrocaudal part of massa intermedia.

Group 2

Cat 51. The boundary between the ventromedial part of the mesencephalic central gray matter and the reticular formation at the level of nucleus oculomtorius.

Cat 39. The ventrolateral part of the mesencephalic central gray matter at the level of nucleus trochlearis.

Cat 2. Cat 7. The boundary between the ventrolateral part of the mesencephalic central gray matter and the reticular formation at the level of nucleus trochlearis.

Cat 7. Cat 14. Cat 17. The reticular formation near the ventral part of the mesencephalic central gray matter at the level of nucleus trochlearis.

Cat 33. Cat 50. The ventrocaudal part of massa intermedia.

Cat 46. Nucleus reuniens.

Group 3

Cat 24. Cat 24. The lateral part of the mesencephalic central gray matter at the level of nucleus oculomotorius.

Cat 5. Cat 5. Cat 7. Cat 10. Cat 25. The lateral part of the mesencephalic central gray matter at the level of nucleus trochlearis.

Cat 6. The ventrolateral margin of corpus quadrigeminum posterior.

Cat 12. The ventrolateral part of the mesencephalic reticular formation caudal to the level of commissura corporis quadrigemini postici.

Cat 29. Cat 32. Cat 32. Cat 44. Cat 45. The medial part of the hypothalamus.

Group 4

Cat 18. Cat 31. Cat 35. Cat 42. The ventral end of the raphe of the mesencephalic central gray matter at the level of nucleus oculomotorius.

Cat 39. Cat 43. The ventromedian part of the mesencephalic central gray matter at the level of nucleus oculomotorius.

Cat 43. The boundary between the ventral part of the mesencephalic central gray matter and the reticular formation at the level of nucleus oculomotorius.

Cat 33. Cat 36. The reticular formation at the level of nucleus oculomotorius.

Cat 42. The reticular formation near the mesencephalic central gray matter at the level of nucleus oculomotorius.

Cat 19. The dorsomedian part of the mesencephalic central gray matter at the level of nucleus trochlearis.

Cat 13. The ventromedian part of the mesencephalic central gray matter at the level of nucleus trochlearis.

Cat 16. The ventrolateral part of the metencephalic central gray matter at the level of nucleus trochlearis.

Cat 16. Cat 25. The ventral part of the mesencephalic central gray matter at the level of nucleus trochlearis.

Cat 19. Cat 20. The aqeductus Sylvii at the level of nucleus trochlearis.

Cat 18. The boundary between the ventromedian part of the mesencephalic central gray matter and the reticular formation at the level of nucleus trochlearis.

Cat 22. The dorsal reticular formation near the mesencephalic central gray matter at the level of nucleus trochlearis.

Cat 10. Cat 19. Cat 19. Cat 20. Cat 20. The reticular formation at the level of nucleus trochlearis.

Cat 6. Cat 23. The boundary between the caudal end of the mesencephalic central gray matter and the reticular formation.

Cat 3. Cat 4. Cat 5. Cat 5. The reticular formation at the caudal end of the midbrain.

Cat 20. Cat 21. Cat 21. Cat 22. The reticular formation near the mesencephalic central gray matter at the caudal end of the mesencephalon.

Group 5

Cat 1. Cat 1. Cat 7. The dorsal part of the mesencephalic central gray matter at the level of nucleus oculomotorius.

Cat 51. The reticular formation near red nucleus at the level of nucleus oculomotorius.

Cat 13. The dorsal part of the mesencephalic central gray matter at the level of nucleus trochlearis.

Cat 19. The ventrolateral part of the mesencephalic central gray matter at the level of nucleus trochlearis.

Cat 8. The boundary between the ventral part of the mesencephalic central gray matter and the reticular formation at the level of nucleus trochlearis.

Cat 6. Cat 11. The reticular formation near the ventrolateral part of the mesencephalic central gray matter at the level of nucleus trochlearis.

Cat 8. The reticular formation at the caudal end of the midbrain.

Cat 11 The ventrolateral part of the reticular formation at the caudal end of the midbrain.

Cat 6. The aqueductus Sylvii at the level of nucleus trochlearis.

Cat 46. The corpus callosum.

Group 6

Cat 6. The dorsal edge of corpus quadrigeminum posticum.

Cat 29. Cat 29. Cat 34. Cat 41. Cat 43. Cat 44. Cat 45. Cat 52. The anterior cingulate gyrus.

The sits of stimulation in group 1 corresponded to the ventral part of the mesencephalic central gray matter, the boundary between this and the reticular formation, and the caudoventral part of massa intermedia. In group 2, stimulated sites were, besides the above mentiond loci, the dorsomedial part of the mesencephalic reticular formation and nucleus reuniens (cf. Fig. 3 and 4). But it is to be noticed that all the cases in which these sites were stimulated did not always

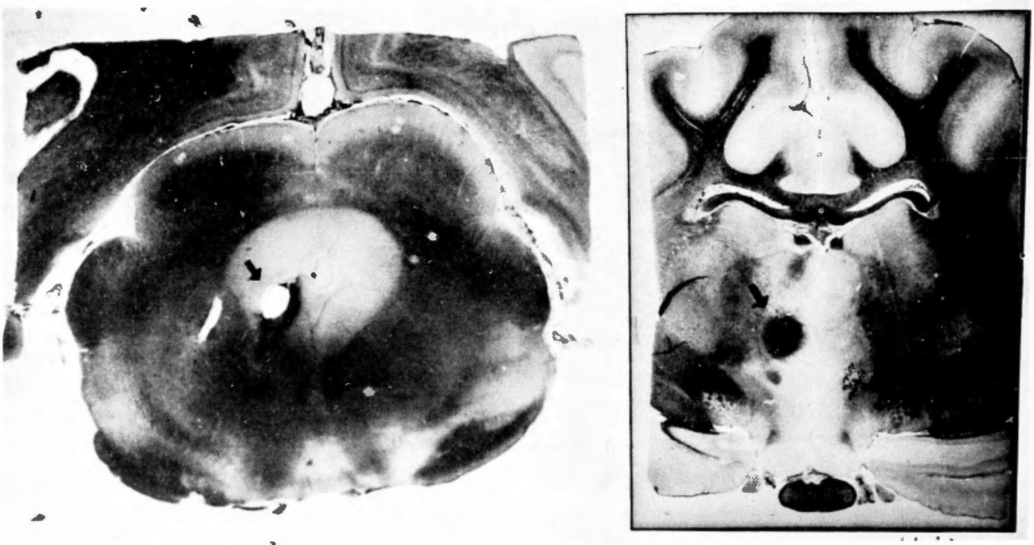


Fig. 3. Sites of stimulation in two cases of group 1.
(A) Cat 17. 1st puncture on the left side. The transverse section of the midbrain. The site of stimulation is shown by arrow.
(B) Cat 49. 1st puncture on the left side. The transverse section of the midbrain. Arrow indicates the site of stimulation.

belong to group 1 or 2.

But in stimulation of other parts of the mesencephalic reticular formation, anterior cinglate gyrus and the hypothalamus etc., there was no animal of group 1 or 2.

The sites of stimulation in group 3 corresponded to the mesencephalic central gray matter, mesencephalic reticular formation, corpus quadrigeminum posticum and the caudomedial part of the hypothalamus, those in group 4 corresponded to the mesencephalic central gray matter, the aqueductus Sylvii and the mesencephalic reticular formation, those in group 5 to the mesencephalic central gray matter, the aqueductus Sylvii, mesencephalic reticular formation, and the corpus callosum, and those in group 6 to corpus quadrigeminum posticum and the anterior cingulate gyrus.

Some remarks will be made in the following about the relations of various

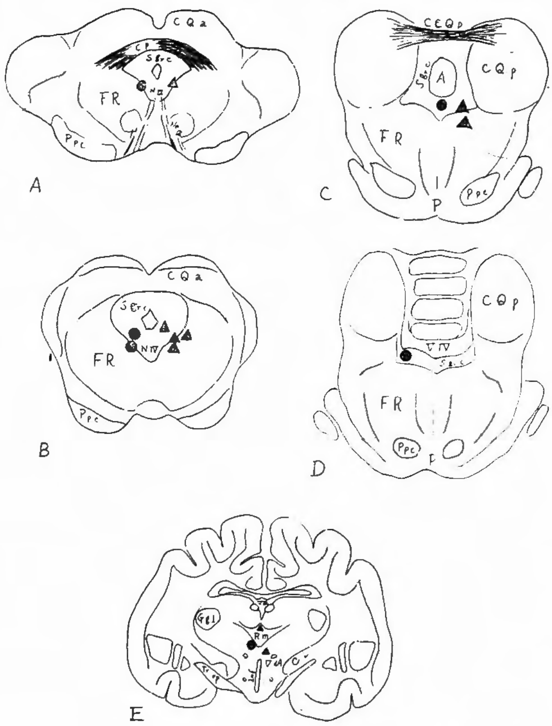


Fig. 4. Sketches showing the sites of stimulation in the cases of group 1 and 2.
A-D : Transverse sections of the midbrain.
E : Transverse section of the diencephalon.
● : Coma. ▲ : Semicoma.

Table 2.

Location of the electrical stimulation	Group	No. of case	Partial sum	Total sum
Central gray matter	1	4	28	69
	2	1		
	3	7		
	4	11		
	5	5		
Boundary between the ventral part of the central gray matter and the reticular formation	1	2	10	
	2	3		
	3	0		
	4	4		
	5	1		
Reticular formation	1	0	26	
	2	3		
	3	1		
	4	17		
	5	5		
Posterior colliculus	3	1	2	
	4	1		
Aqueductus	4	2	3	
	5	1		

Incidennce of each type of reactions as seen in stimulation of various mesencephalic structures.

mesencephalic sites to the types of reaction on stimulation (cf. Table 2).

In stimulation of the mesencephalic central gray matter, various types of reaction were seen, the animals belogning to group 1, 2, 3, 4 and 5. Coma and semicoma in group 1 and 2 were elicited by stimulation of the ventral part of it, sham rage in group 3 was elicited by stimulation of the lateral part, kinetic excitation in group 4 by stimulation of the midline and in the ventral region, and convulsion in group 5 by that of the dorsal part. In stimulating the mesencephalic central gray matter at the level caudal to commissura corporis quadrigemini postici, various responses could be elicited from one and the same area.

Incidence of elicitation of coma by stimulation of the ventral part of the mesencephalic central gray matter was about 22%, and that of elicitation of coma and semicoma was about 37%. In 9 out of these cases the ventromedian part of the central gray was stimulated with resulting kinetic excitation in 7 and coma and semicoma only in 2. Thus stimulation of the ventral part of the central gray excluding the median portion induced coma in 22% and coma and semicoma in 44% of the cases.

(10) Comparison was made between the effect of the gradual stimulation of increasing intensity and that of the sudden stimulation of consistent intensity (cf.

Table 3.

Group	No. ef cat	Conditions	Result (grouping)
1	8	4v. 2mA (6v. 4mA)	1
	17	1v. about 0.01mA (1v. about 0.01mA)	1
	25	4v. 2mA (4v. 2mA)	1
	32	6v. 1mA (6.5v. 2.5mA)	1
	48	3.4v. 1mA (5.5v. 2mA)	1
	49	2.7v. 1mA (2.7v. 1mA)	1
2	33	4v. 2mA (4v. 2mA)	2
	46	2v. 0.5mA (2v. 0.25mA)	2
	51	1.8v. 0.5mA (3v. 1mA)	5

In each case coma or semicoma was elicited at first by gradually increasing stimulation. Parameters of stimulation at the time when coma or semicoma was induced are shown in parenthesis. When the animal regained full responsiveness, abrupt stimulation of constant intensity was made to the same loci using parameters shown without parenthesis.

Table 3).

Of 9cases in which coma or semicoma was induced by the gradually increasing stimulation, the same type of response was induced by the sudden stimulation in 8 cases.

Thus, it was found that the coma or semicoma with no convulsive phase (in group 1 and 2) could be elicited not only by the gradually increasing stimulation, but also by the sudden stimulation.

The same was true of groups 3, 5 and 6, but many cases of group 4 showed the preceding convulsive phase when the sudden stimulation was made.

(11) Square pulses were used for stimulation in some cases instead of alternating current, and the same results were obtained when square pulses were of 60 per second (cf. Table 4).

Table 4.

No. of cat	Group	Conditions	Result (grouping)
17	1	4v. 1msec	1
17	2	3.2v. 1msec	2
39	2	15v. 0.2msec	2
50	2	10v. 1msec	2

Conditions of square pulse stimuli applied to the sites where gradually increasing stimulation induced coma or semicoma.

(12) Electroencephalographic findings.

Surface EEGs were recorded in some cases of group 2 (semicoma) during stimulation by square pulses (cf. Fig. 5). As seen in the figure, no eminent slow wave appeared, but after-discharge-like-wave was observed during semicoma.

(III)

From the above results, it became clear that coma and semicoma could be

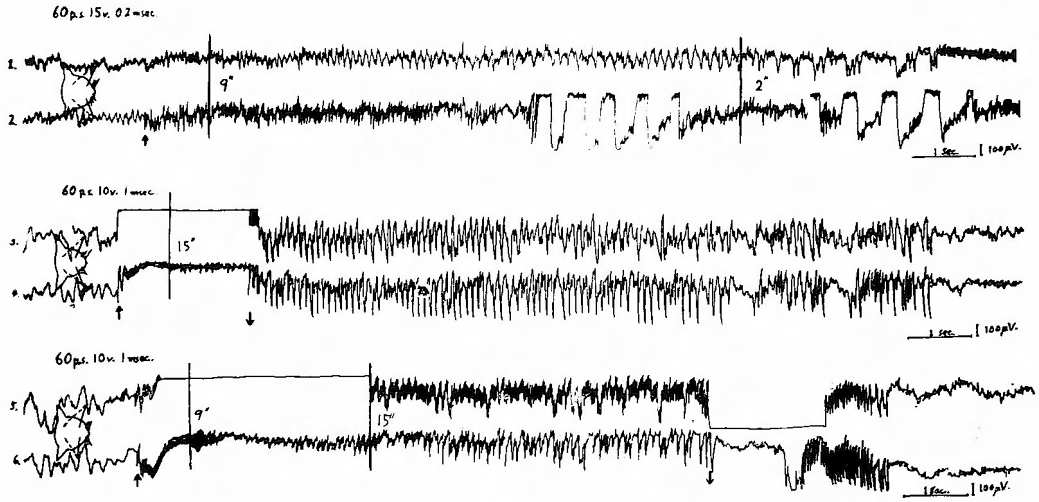


Fig. 5. Strips 1 and 2: cat 39. Square pulse stimulation (60 per sec., 15 volts, 0.2 msec) of the mesencephalic central gray matter. Semicoma was indusced.
Strips 3-6: cat 50. Square pulse stimulation (60 per sec., 10 volts, 1 msec) of massa intermedia.
Semicoma was induced. Time in parenthesis indicate period of partial abridgment of the record.

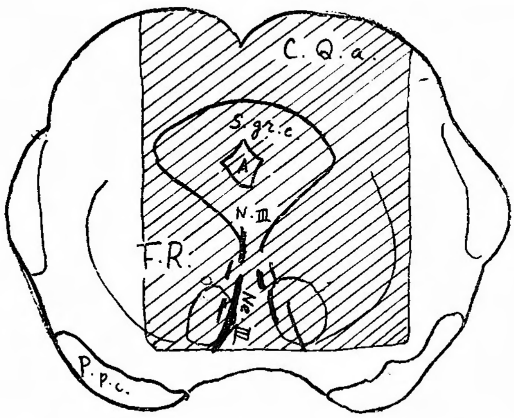


Fig. 6. Transverse section of the midbrain at the level of nucleus oculomotorius, showing the extent of the lesion effected by the partial transection in cat 68.

produced in some cases by alternating current stimulation of the mesencephalic central gray matter. Thus, an attempt was made to transect the rostral part of the midbrain, supposing that this procedure might exert some foundamental influence on the stimulation effect.

(1) Partial transection.

In some cases of groups 1, 2, 3, 4 and 5, where electrical stimulation was given to the mesencephalic central gray matter, partial transection covering the mesencephalic central gray matter (cf. Fig. 6) was done cranial to the stimulation point. Electrical stimulation was then made again, but there wes almost no change in the effect of stimulation as compared with that before transection.

(2) Total transection.

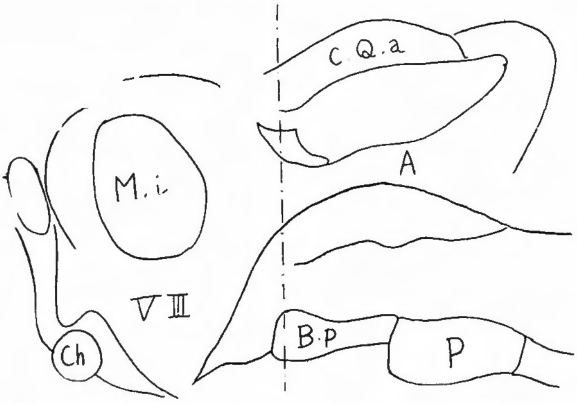
Total transection of the midbrain (cf. Fig. 7) was done in some cases of groups 1 and 2.

After the transection the cat became quiet, but all nociceptive reflexes were preserved; the animal screamed by the electrical stimulation of the sciatic nerve.

In partial or total transection, when it was done rapidly, the cat suddenly fell

Fig. 7.

(A) Transverse section of the rostral part of the midbrain showing the extent of the lesion effected by the total transection.



(B) Midsagittal reconstruction of the brain stem. The plane of transection is shown.

into coma for some moments.

Cat 68. male, 3 kg.

Partial transection of the brain stem was made rapidly at the level of oculomotor nucleus as shown in Fig. 6. Instantly the cat showed tonic stretching of the four limbs for some moments and the state corresponding to coma or semicoma ensued for 15 minutes, and finally normal responsiveness was restored.

After the mesencephalic transection had been done, electrical stimulation was carried out through the electrodes previously inserted and fixed in a locus in the central gray where a stimulation study had been done before the transection.

Coma or semicoma was induced by the stimulation in the same way as before transection, and the cat did not cry, unless high voltage square pulses were used for stimulation of the sciatic nerve.

Cat 85. Female, 26 kg. 1st puncture on the left side of the midbrain.

The site of electrical stimulation: the mesencephalic central gray matter at the level of nucleus trochlearis.

Coma was elicited by the electrical stimulation with the intensity of about 2 volts and 0.2 mA. As soon as the stimulation ceased, the cat mewed lightly, and nociceptive reflexes reappeared. Then, total transection was done at the rostral end of the midbrain. After 30 minutes, all nociceptive reflexes returned, and the cat screamed when square pulse stimulation was afforded to the sciatic nerve with the intensity of 10 volts, the frequency of 60 per second and the pulse duration of 1 msec. The cat fell into coma when the second electrical stimulation of the central gray was made with the intensity of 3.5 volts and 0.4 mA. During coma, the cat screamed when strong square pulse stimulation was afforded to the sciatic nerve with the intensity as high as 35 volts but with the same frequency and pulse duration as in the previous test.

The site of transection confirmed at autopsy: the frontal plane passing through the rostal end of corpus quadrigeminum anticum and the exit point of n. oclomotorius from the brain stem (cf. Fig. 7).

Cat 88. Female, 2.5 kg. 1st puncture on the left side of the midbrain.

The verified site of electrical stimulation: the mesencephalic central gray matter at the level of nucleus trochlearis.

Semicoma was elicited by electrical stimulation of about 4 volts and 0.4 mA. After the transection, the cat screamed when stimulation was made to the sciatic nerve with square pulses of from 0.2 to 0.4 volts, 60 per second and 1 msec in pulse duration. The response of the sham rage type was elicited by the second electrical stimulation with 60 p. s. AC of 0.5 volts and about 0.01 mA. Then the electrodes were inserted more deeply by about 0.2 cm. At this time, the cat fell into semicoma when electrical stimulation of 1.5 volts and about 0.01 mA was effected. During semicoma the cat mewed faintly when stimulation was made to the sciatic nerve with square pulses of 30 volts.

The verified site of transection: Same as in case 85.

In cases 85 and 88 the complete electronarcosis was induced by the extraduaral electrical stimulation before as well as after mesencephalic transection.

From the above results, it is apparent that coma or semicoma can be elicited both by the extradural electrical stimulation and by the directly applied electrical stimulation of the mesencephalic central gray matter, even which total transection had been made at the rostral end of the midbrain.

DISCUSSION

The electronarcosis was induced, though not regularly, by stimulation of certain parts of the brain stem; the caudoventral part of massa intermedia, the ventral part of the mesencephalic central gray matter, the boundary between the central gray and the reticular formation, and the dorsal reticular formation near the central gray matter. The narcosis evoked from the last mentioned locus was not so deep as that from the other parts. Thus it is likely that the electronarcosis is more closely related to massa intermedia and the ventral mesencephalic central gray matter than to the mesencephalic reticular formation.

The state of electronarcosis grossly corresponds to coma or semicoma, and is characterized by loss of all nociceptive reflexes, reduction in muscle tone, and lack in voluntary and involuntary movements of the body trunk and the four limbs.

But, it is to be noticed that coma or semi-coma was regularly induced by the extradual electrical stimulation, whereas it was less frequently induced by the electrical stimulation of the midbrain.

In the sham rage or the kinetic excitation type, the animal screamed and/or writhed (without any concomitant convulsive movements of the body), but showed only partial impairment nociceptive refleces. These states are not unlike to the excitement stage of general anesthesia in which consciousness seems to be impaired to a certain degree. The two types were induced by stimulation of the mesencephalic central gray matter or a part of the mesencephalic reticular formation, closely neighboring the central gray matter. These areas are included in the regions from which coma could be induced. On the other hand, there were many cases in which sham rage and kinetic excitation were elicited by stimulation of the reticular formation fairly apart from the mesencephalic central gray matter.

It should be noted that the extradural electrical stimulation did not effect these types of reaction, but only coma and semicoma. The reason may be in that the extradural stimulation may widely excite a large part of the midbrain. This assumption is based on the fact observed by IKUSHIMA that coma was produced by the chemical stimulation with a large amount of diluted sublimate solution injected in a wide extent of the mesencephalic reticular formation, whereas the stimulation (chemical or electrical) of a small extent of this structure predominantly induced excitement of the reticular activating system accompanied by behavioral arousal as reported by Magoun.

In our midbrain-animal it was confirmed that all reactions were nearly the same as before transection; nociceptive reflexes were preserved, sham rage or kinetic excitation could be caused by stimulation of the midbrain caudal to the transection, and stimulation of the mesencephalic central gray matter could elicit behavioral changes of the type of coma or semicoma.

Therefore it seems that our experimental coma induced by mesencephalic stimulation has nothing to do with the cerebral cortex and with the diffuse thalamocortical projecting system of Morison and Dempsey, as well as with the ascending reticular activating system of Magoun. It rather seems that the portion of the brain stem extending from massa intermedia to the ventral mesencephalic central gray matter relates closely to the electronarcosis or the coma (unresponsiveness to nociceptive stimuli) reported here.

In summarizing, the electronarcosis, or coma as well as semicoma seen in groups 1 and 2 of our experiments, is effected by neural mechanisms of the midbrain and nervous structures caudal to it. Especially the ventral area of the mesencephalic central gray matter seems to play the most important part in these mechanisms, in which the mesencephalic reticular formation etc. more or less participate too. However it is possible that coma is caused more easily by stimulating the whole extent of the midbrain, than a certain circumscribed locus in the midbrain.

CONCLUSION

The disturbance of consciousness dealt with in this paper is that of the consciousness of lower level (i. e. of reflex nature), and can be effected by the alternating current stimulation of the ventral part of the mesencephalic central gray matter. As to the disturbance of consciousness of higher level nothing can be discussed from the results of our experiments.

Our conclusion is that the ventral mesencephalic central gray matter plays an important role in the disturbance of lower consciousness.

References

1) Araki, C., T. Taketomo and T. Toda: Coma puncture. Acta Scholae Med. Univers. Kioto Jap., 27, 205-214, 1949. 2) Akert, K., W. P. Koella and R. Hess, Jr., Sleep produced by electrical stimulation of the thalamus. Am. J. Physiol., **168**, 260-267, 1952 3) French, J. D., F. K. Vcn Amerongen and H. W. Magoun: An activating system in brain stem of monkey, A. M. A. Arch. Neurol. Psychat., **68**, 577-590 1952. 4) Gerard, R. W., W. H. Marchall and L. J. Saul: Electlical activity of the cat's brain. Arch. Neurol. Psychiat., **36**, 675, 1936.

5) Girndt, O.: Die Ermittelūng der Wirkūngsstärke von Schlafmitteln mit Hilfe der Körperstell-und Labyrinthreflexe. I. Arch. f. exp. pathol. ū. Pharmakol., 164, 118-157. 1932.

6) Hanbery, J., C. Ajmone-Marsan and M. Dilworth: Pathways of nonspecific thalamo-cortical projection system. EEG. Clin. Neurophysiol., **6**, 103-118, 1954. 7) Hess, W. R.,: The diencephalic sleep centre. Brain mechanisms and consciousness. A symposium organized by the council for international organization of medical science. 1954.

8) Ikushima, H., 1955: Uncousciousness by injection of dilute solution of corrosive sublimate. Presented at the 52nd Congress of Japan Psychoneurological Society, Kioto.

9) Ishii, S.: Coma puncture (monograph), Kioto. 1944. 10) Jasper, H.: Diffuse projection systems: the integrative action of the thalamic reticular system. EEG Clin. Neurophysiol., 1, 405-420, 1949. 11) Jasper, H., C. Ajmone-Marsan and J. Stoll: Coriticofugal projections to the brain stem. A. M. A. Arch. Neurol. Psychiat., 67, 155-171, 1952. 12) Magoun, H. W.: An ascending reticular activating system in the brain stem. Arch. Neurol. Psychiat., Chicago, 67, 145, 1952. 13) Magoun, H. W. 1950: Caudal and cephalic influence of the brain stem reticular formation. Physiol. Rev., **30**, 459-474, 1950. 14) Matsunaga, M.: Experimental studies on coma induced by stimulation of various parts of the brain in cat. Being preparted for publication. 15) Matsunaga M, K. Sakata, H. Ikushima and S. Asai: Coma induced by chemical and electrical stimulation of brain stem. Presented at the 13th Congress of Japan Neurosurgical Society, Tokyo. 1954. 16) Mc Lardy, T., 1951: Diffuse thalamic projection to cotex. An anatomical critique. EEG Clin. Neurophsiol., **3**, 181-188.

17) Morison, R. S. and E. W. Dempsey: A study of thalamo-cortical relations. Am. J. Physiol., **135**, 281-292, 1942. 18) Moriyasu, H.: Unconsciousness evoked by stimulation of lower brain stem. Presented at the 53rd Congress of Japan Psychoneurological Society, Tokyo. 1956. 19) Nagai, T.: Cerebral blood flow during coma induced by the stimulation of the periaqueductal gray matter (coma puncture). Acta Scholae Med. Univers. Kioto Jap., **31**, 193-214, 1954.

20) Niimi, K.: Comparative anatomical study of the thalamus of mammals, Brain-Reserches, 7, 88-99, 1950. 21) Niimi, K.: Zūr vergleichenden Cytoarchitektonik der vorderen, medianen ūnd medialen Kerngrūppe des Sehhügels des Meschen. Acta Scholae Med. Univers. Kioto Jap., **27**, 116-132, 1949. 22) Sakata, K.: Electroencephalographic studies on coma induced by stimulation of various parts of the brain in cat. Being prepared for publication.

23) Schiller, F.: Consciousness reconsidered. Arch. Neurol. Psychiat., Chicago **67**, 199, 1952.

24) Winkler, C. and A. Potter: An anotomical guide to experimental researches on the cat's brain. W. Versluys, Amsterdam. 1914

25) Yabuno, S.: Coma puncture by means of nicotinization. Acta Scholae med.' Univers. Kioto Jap, **32**, 32-51, 1954. 26) Yoshii, N.,: Physiological researches of Eilepsy, No-to-shinkei, 5, 57, 1953.

Abbreviations in Figures

A	Aqueduct
B. P	Basis pedunculi
C. h	Chiasma nervi optici
c. i	Capsula interna
C. Q. a	Corpus quadrigeminum anticum
C. Q. P	Corpus quadrigeminum posticum
C. C. Q. P	Commissura corporis quadrigemini postici
C. P	Commissura posterior
F. R	Formatio reticularis
G. g. l	Ganglion geniculatum laterale
Inf	Infundibulum
M. i	Massa intermedia
N. III	Nucleus oculomotorius
N. IV	Nucleus trochlearis
Ne. III	N. oculomotorius
P	Pons
P. P. c	Pes pedunculi cerebri
R. m	Nucleus reuniens medianus
S. gr. c	Substantia grisea centralis
Tr. op	Tractus opticus
V. III	Ventriculus III

V. IV	Ventriculus IV	V. dA	Fasciculus Vicq d' Azyr

和文抄録

脳幹部を直接刺戟する電気麻酔実験

京都大学医学部外科第1講座（荒木千里教授 指導）

浅 井 茂 三

私達は吉井氏の無痙攣電気麻酔を無麻酔猫の脳の各所に直接適用する実験を行い，又中脳吻側部に横完全切断を加えた猫で，同様の電気刺戟実験を中脳に於て行い，検討を加えた．その結果よりして，電気麻酔状態は中脳以下の機構によるもので，中脳中心灰白質が特にその機構に重要な部位を占めるが，中脳網様織等も関係している．併し之等個々の部分が刺戟される場合よりも，全体として中脳が広く刺戟された場合に電気麻酔状態が起り易いものゝ様に思われる．